Please cancel claims 2, 13, 51, 59, 64 and 70 without prejudice.

REMARKS

Claims 1, 3-12, 14-40, 46-52, 56-58, 60-63, 65, 69-70 and 73-75 are pending. Claims 2, 13, 59, 64 and 70 have been canceled without prejudice. Applicants reserve their rights to prosecute subject matter of canceled claims in subsequent applications.

Claim 49 has been amended to delete recitation of "and progeny thereof derived from."

Claim 56 has been amended to be in proper dependent format to be dependent upon claim 61 instead of canceled claim 55.

Claim 69 has been amended to recite a DNA construct comprising a first and second DNA sequence capable of expressing in a cell a sense and antisense fragment of a viral genome or portion thereof, and to delete recitation of target gene. Support is in the specification on page 3, lines 21-23 and page 10, line 5.

No new matter has been added by these amendments.

Claim Objections

Claims 2, 13 and 64 have been objected to as being failing to further limit their parent claims. In response, claims 2, 13 and 64 have been canceled without prejudice.

These amendments obviate these objections, and Applicants request their withdrawal.

Section 112 Rejection of claims 56-58, 60 and 61

Claims 56-58, 60 and 61are rejected under 35 USC § 112. second paragraph, as allegedly being indefinite for failing to particularly point out and claim the instant invention for being dependent upon cancelled claim 55. In response, claim 56 has been amended to depend on claim 61 instead of canceled claim 55. Claims 60 and 61 are dependent upon claim 59 which is dependent upon claim 12. These claims are in proper dependent form.

Section 112 Rejection of Claims 1-10, 11-40, 46-52, 56-65, 69, 70 and 74-75

Claims 1-10, 11-40, 46-52, 56-65, 69, 70 and 74-75 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons stated in the last Office Action for claims 63-70 and 72. In particular, the Office Action contends that the specification on

"pages 26-43 does not provide information regarding the sequences and functions of all the sequences encompassed by the claims. . . [and] does not provide description of the portions of viral genomes, which encompass non-coding sequences, that are functional with the claimed invention."

Applicants respectfully disagree with this rejection.

The legal standard for meeting the written description requirement under section 112, first paragraph, is whether "the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar,* 935 F.2d 1555, 1563-64, 19 USPQ2d 1111,1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed.

The specification as filed meets the requirements for written description of the present invention. The invention encompasses methods of altering or decreasing the expression of a viral genome or portion thereof by either introducing sense and antisense RNA molecules or a DNA construct comprising a first and second DNA sequence capable of expressing sense and antisense RNA fragments of a viral genome or portion thereof.

The present invention describes the use of dsRNA molecules which comprise a sense and antisense RNA for a target gene of interest, more specifically, a virus or portion of a virus as presently claimed. The crux of the invention is that the nucleotide sequence and function thereof can be any gene of interest or virus or portion thereof for which one seeks to alter or decrease the expression. The important aspect is that the RNA molecule(s) form a dsRNA structure. By "altering the expression of the viral genome or portion thereof" is described on page 12 as "typically understood that accumulation, replication or movement of the virus or a portion thereof, e.g., a RNA, DNA or protein portion of the virus, in the cell is affected."

In particular, on pages 17-19, the specification describes that dsRNA is used to control any number of viruses of interest using sequences from such viruses or related viruses. Preferred sequences are either from protein coding regions or portions thereof, or sequences including portions of the viruses not translated into proteins, e.g. 5' or 3' untranslated regions (page 18).

As described above, the specification clearly allows a person of ordinary skill in the art to recognize what has been claimed.

Section 112, first paragraph, Rejection of Claims 1-40, 45-52, 56-65, 69, 70 and 73-75

Claims 1-40, 45-52, 56-65, 69, 70 and 73-75 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, the Office Action alleges that the instant specification does not demonstrate that the expression of the sense and antisense RNA molecules actually led to alteration of gene expression in cells for reasons set forth in the Office Action dated January 19, 2001. Further, the Office Action contends that the Declaration of Jan Gielen did not address the issues of enablement with regard to all virus genomes, or any portion thereof, nor non-plant cells and non-plant viruses.

Applicants respectfully disagree with this rejection.

Enablement doesn't require detailed description of every possible embodiment

There is no requirement in section 112, first paragraph, that the specification provide a detailed description of every possible embodiment covered by the claims. The Examiner is respectfully referred to the controlling opinion in In re Goffe, 191 USPQ 429, 431 (1976), which makes clear that a claim may cover embodiments not actually reduced to practice prior to the filing date of the application:

> For all practical purposes, the Board would limit appellant to claims involving the specific materials disclosed in the examples, so that a competitor seeking to avoid infringing the claims would merely have to follow the disclosure in the subsequently-issued patent to find a substitute. However, to provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specific for "preferred" materials in a process . . . would not serve the constitutional purpose of promoting progress in the useful arts.

The claimed methods call for expression of sense and antisense RNA molecules comprising nucleotide sequences from a viral genome or portion thereof. This RNA or RNA expressed from DNA constructs confers resistance or tolerance to a virus. The critical aspect of the method is not the nature of the viral sequence, but rather the use sense and antisense sequences obtained or derived from a viral sequence of interest.

In line with the holding in Goffe, supra, it does not serve the constitutional purpose of promoting progress in the useful arts if others may take Applicants' example of using dsRNA for

altering virus resistance in a dicotyledonous plant cell and substitute a sequence from another virus to obtain altered virus resistance to another virus in another cell type. The Examiner is fully aware that how to substitute one viral sequence for another in a dsRNA is within the knowledge of one of ordinary skill in the art and does not require "undue experimentation."

The specification as filed fully enables the present invention.

Applicants respectfully disagree with the Examiner's conclusion on page 5 of the Office Action that the present invention would not reduce expression of all viral genomes that have PTGS suppressors. Vionnet et al., on pages 14151-152 describes tissue specific patterns of PTGS suppression of a reporter gene, GFP upon infection with viruses encoding proteins that are suppressors of RNA-mediated defense (RMD) (page 14151, col. 1-2). In fact, Vionnet shows only that the pattern of PTGS is tissue or leaf-age specific. Vionnet does not describe that expression of a viral genome or portion thereof of a virus that encodes a suppressor, fails to alter the resistance or susceptibility of the plant to viral infection. Neither the Examiner nor the reference Vionnet et al. demonstrates that the present invention would fail to reduce expression of a viral genome having a suppressor.

The Applicants also disagree with the ground of rejection based on the reference of Montgomery et al. Numerous references cited below, demonstrate that dsRNA or RNAi has been demonstrated in mammalian cell types. Most important, virus inhibition by RNAi has been demonstrated in mammalian cells, see #310, John et al., *Degradation of hepatitis C virus RNA by short double-stranded RNA in mammalian cell culture,* which states that virus degradation was observed following introduction of dsRNA.

See also, Elbashir et al., *Duplexes of 21-nucleotide RNAs mediated RNA interference in cultured mammalian cells*, Nature 411:494-498 (2001) (demonstrating RNAi in human cell lines human embryonic kidney (293) cells and HeLa cells using 21 and 22-nucleotide siRNAs that circumvent the PKR response); Paddison et al., *Stable suppression of gene expression by RNAi in mammalian cells*, PNAS USA 99(3):1443-48 (2002) (showing cultured murine cells specifically silence gene expression upon treatment with long dsRNAs (approx. 500 nts); Wianny et al., *Specific interference with gene function by double-stranded RNA in early mouse development*, Nature Cell Biol. 2:70-75 (1999); Svoboda et al., *Selective reduction of dormant maternal mRNAs in mouse oocytes by RNA interference*, Development 127:4147-56 (2002); and Bahramian et al., *Transcriptional and posttranscriptional silencing of rodent α1(I) collagen by a homologous transcriptionally self-silenced transgene*, Mol. Cell Biol. 19(1):274-283. See also Abstracts from Keystone Symposium, Feb. 21-26, 2002, #214, McManus et al., *Mechanism for RNA interference in Murine T-lymphocytes*; #217, Pachuk, *DsRNA mediated post-transcriptional gene silencing and the interferon response in human cells and an adult mouse model;* #303, Cabello et al., *RNAi in*

transgenic mice;; #312, Lewis et al., *Specific inhibition of gene expression in post-natal mammals using small interfering RNAs;* #306, Elbashir et al., *Analysis of mammalian gene function using siRNA duplexes*; and #307, Geick et al., *Specific inhibition of cancer-related target gene expression by short double-stranded RNA*. (Attached as Exhibits 1-6).

While it is true that these literature articles are dated after the filing date of the parent application, they represent evidence of the operability of the teachings of the application. The specification is enabling for the broad scope for which patent protection is being sought and this broad scope was accepted as such by others in the same field, such as those listed above, who subsequently found similar results as did Applicants, using a dsRNA or RNAi sequences in mammalian cells to reporter genes or to the virus hepatitis C. As a matter of law, the references cited by applicants may be considered as evidence of the level of skill at the time of the application and as evidence that the disclosed invention would have been operative. Gould v. Kreig, 822 F.2d 1074, 1078 (Fed. Cir. 1987), citing In re Hogan, 559 F.2d 595, 605, 194 USPQ 527, 337 (CCPA 1977).

Regarding the rejection of claims 56-58, Applicants respond as follows. Claims 56-58 are ultimately dependent on claim 12 which are directed to methods comprising introducing DNA sequence into cells that would be inherited. However, claim 49 (ultimately dependent upon claim 1) has been amended to recite a plant comprising the plant cell of claim 47. Claim 51 has been canceled without prejudice.

The above remarks, declaration, and amendments overcome and /or obviate the above grounds for rejection, and Applicants respectfully request its withdrawal.

Section 112, first paragraph, Rejection of Claim 70

Claim 70 remains rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention for reasons stated in the January 19, 2001 Office Action. In particular, claim 70 is still drawn to alteration of a target gene. Claim 70 has been canceled without prejudice.

Claims Rejections under 35 USC §103

Claims 1-30, 33-40, 46-52, 56-65, 70, and 73-75 are rejected under 35 USC § 103(a) as allegedly being unpatentable over Sijen et al. in view of Fire et al., Applicants admitted state of the prior art and Keddie et al. The Office Action contends that it would have been obvious for one or ordinary skill to stably transform a plant cell with DNA construct that comprises DNA encoding sense and antisense RNA fragments following the demonstration of Fire.

Applicants disagree with this rejection.

A finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere, 383 U.S. 1 (1966). The relevant inquiry is whether the prior art suggest the invention, and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. In re O'Farrell 853 F.2d 894, 903 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art and not in the Applicants' disclosure. In re Vaeck 947 F.2d 488 (Fed. Cir. 1991).

Most important, "obvious to try" a particular experiment or combination is not the appropriate standard for determining obviousness. In re Lindell, 385F.2d 453, 15 U.S.P.Q. 521 (C.C.P.A. 1967).

The cited references do not make obvious the presently claimed invention. Fire et al., at page 810, merely proposes that "RNA interference might also operate in plants" but provides no reasonable expectation of success. Also, Sijen et al. provide no reasonable expectation of success that sense and antisense constructs would necessarily provide resistance to viruses.

The above remarks overcome this rejection and Applicants request its withdrawal.

CONCLUSION

The above amendments and remarks overcome or obviate the above rejections and put the application in form for allowance.

The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.17 which may be required, or credit any overpayment, to Account No. 50-1744 in the name of Syngenta.

A duplicate copy of this letter is provided for charging purposes.

Respectfully submitted,

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Date: April 3, 2002

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IN THE CLAIMS:

Please amend the claims as follows:

49. (amended) A plant [and the progeny thereof derived from] comprising the plant cell of claim 47.

69. (twice amended) A DNA construct comprising a first DNA sequence capable of expressing in a cell a sense RNA fragment of a viral genome or portion thereof [target gene] and a second DNA sequence capable of expressing in said plant cell an antisense RNA fragment of said viral genome or portion thereof [target gene], wherein said sense RNA fragment and said antisense RNA fragment form a double-stranded RNA molecule, wherein said DNA construct further comprises a bi-directional promoter operably linked to said first DNA sequence and to said second DNA sequence.

Please cancel claims 2, 13, 51, 59, 64 and 70 without prejudice.